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Review
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Pathophysiology, Clinical Importance, and Management of Neurogenic Lower Urinary Tract Dysfunction Caused by Suprasacral Spinal Cord Injury

H.Z. Hu, N. Granger, and N.D. Jeffery

Management of persistent lower urinary tract dysfunction resulting from severe thoracolumbar spinal cord injury can be challenging. Severe suprasacral spinal cord injury releases the spinal cord segmental micturition reflex from supraspinal modulation and increases nerve growth factor concentration in the bladder wall, lumbosacral spinal cord, and dorsal root ganglion, which subsequently activates hypermechanosensitive C-fiber bladder wall afferents. Hyperexcitability of bladder afferents and detrusor overactivity can cause urine leaking during the storage phase. During urine voiding, the loss of supraspinal control that normally coordinates detrusor contraction with sphincter relaxation can lead to spinal cord segmental reflex-mediated simultaneous detrusor and sphincter contractions or detrusor-sphincter dyssynergia, resulting in inefficient urine voiding and high residual volume. These disease-associated changes can impact on the quality of life and life expectancy of spinal-injured animals. Here, we discuss the pathophysiology and management considerations of lower urinary tract dysfunction as the result of severe, acute, suprasacral spinal cord injury. In addition, drawing from experimental, preclinical, and clinical medicine, we introduce some treatment options for neurogenic lower urinary tract dysfunction that are designed to: (1) prevent urine leakage arising because of detrusor overactivity during bladder filling, (2) preserve upper urinary tract integrity and function by reducing intravesical pressure and subsequent vesicoureteral reflux, and (3) prevent urinary tract and systemic complications by treating and preventing urinary tract infections.

Key words: Cystometry; Dog; Spinal; Urinary; Urodynamics.

Management of lower urinary tract dysfunction is frequently a long-term problem in pet dogs that incur severe spinal cord injury. Currently, management consists primarily of regular manual bladder expression, periodic urinalysis, and bacteriological culture, plus symptomatic antibiotic treatment and, less commonly, prophylactic antiseptic treatment, dietary supplements, or both.[1–4] These standard management strategies aim to address inappropriate reflex urine voiding and the inability to initiate voluntary bladder emptying that can result in recurrent urinary tract infections, which have the potential to cause life-threatening ascending pyelonephritis. In this review, we discuss the neurologic pathways involved in normal lower urinary tract function and how these pathways can be altered by spinal cord injury and result in lower urinary tract dysfunction. In addition, we outline how these disease-associated changes can be diagnosed and monitored using cystometry. Lastly, drawing from experimental, preclinical, and clinical medicine, we introduce some additional management considerations and treatment options for neurogenic lower urinary tract dysfunction.

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Functional Anatomy and Neurologic Pathways of the Lower Urinary Tract

The lower urinary tract consists of an expandable reservoir, the urinary bladder, that stores urine until periodic voiding and an outlet consisting of the bladder neck, urethra, and internal and external urethral sphincters that permits bladder emptying when intravesical pressure or volume reach specific sensory thresholds. In dogs and cats, the reciprocal mechanisms involved in urine storage and voiding are mediated by afferent and efferent impulses that travel in three paired peripheral nerves, namely the pelvic, hypogastric, and pudendal nerves, and are coordinated by segmental spinal cord reflexes and supraspinal pathways involving the brainstem and cerebral cortex (Fig 1).[5,6]

The sensory fibers that innervate the lower urinary tract extend from the bladder wall, bladder neck, and urethra to the spinal cord via lumbosacral dorsal root ganglia of the pelvic, hypogastric, and pudendal nerves and convey sensory information regarding the degree of bladder distension.[6] The relative proportions of sensory information from the lower urinary tract carried in each of these three paired nerves vary between species.[5–8] For instance, in cats, sensory fibers arising from the bladder wall stretch receptors and the urethra mainly travel within the pelvic and hypogastric nerves;[7] whereas in dogs, sensory input from the bladder wall stretch receptors is carried primarily by the pelvic nerves to the spinal cord.[8] In both species the

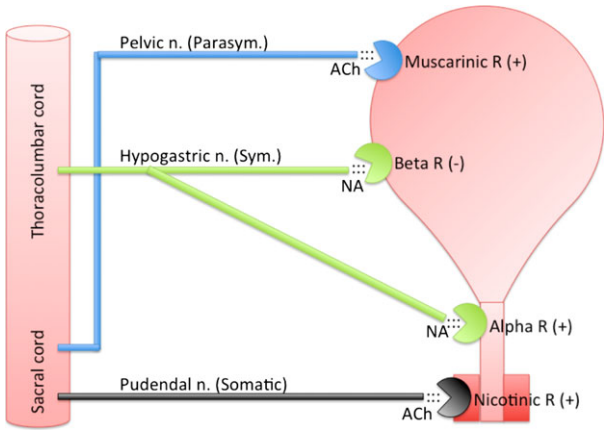

Fig 1. Lower urinary tract innervation and neurotransmitters. Afferents and efferents travel in paired pelvic, hypogastric, and pudendal nerves. Parasympathetic and somatic neurotransmission are mediated by cholinergic fibers; sympathetic function is mediated by adrenergic fibers.

hypogastric nerves relay information regarding bladder overdistension.[9] Further distinctions also exist regarding the specific spinal cord segments that receive the sensory input from the lower urinary tract delivered by the three paired peripheral nerves; for instance, the hypogastric nerves reach the spinal cord at L2–L5 in cats[10] and L1–L4 in dogs.[9]

In species including cats, dogs, rats, and humans, under normal circumstances, myelinated A-delta fiber mechanoreceptors in the bladder wall produce graded trains of activity in response to bladder distension during the storage or filling phase.[6,11–13] The A-delta fiber receptors can change activity in response to noxious stimuli or when spikes of intravesical pressure ~6.8–20.4 cmH_2O or 5–15 mmHg above resting level occur.[11,12] These normal mechanisms, when disrupted, can lead to a series of clinical and functional anomalies.[11,13–15] In certain species such as the rats, a different class of bladder wall receptors, impulses from which are carried by unmyelinated C-fibers, also detect gradual bladder distention during the storage phase, as well as noxious stimuli.[14,15] In contrast, in humans and cats, C-fiber afferent input is normally functionally masked by A-delta afferent input, which renders the C-fiber afferents functionally silent and unresponsive to gradual physiologic bladder distension during filling.[11,12,14,15]

Axons that normally respond to bladder distension, primarily those that carry sensory information from the A-delta fiber mechanoreceptors, project to various spinal cord regions including the dorsal commissure, the superficial dorsal horn of the lumbosacral spinal cord, and the sacral parasympathetic nucleus.[15] A-delta fiber input ascends in the spinal cord via the spinothalamic and spinobulbar tracts; the former reaches the thalamus and subsequently the suprathalamic centers such as the cerebral cortex, thereby conveying conscious sensory information, whereas the latter reaches the pontine micturition center in the brainstem.[6] Unmyelinated C-fibers typically convey sensory information such as autonomic regulation of micturition that does not undergo conscious processing and this information ascends in the spinomesencephalic, spinoreticular, and spinohypothalamic tracts to reach subthalamic structures in the brain.[6,14,15]

Two brainstem nuclei, the pontine micturition center and the periaqueductal gray, receive afferent input primarily from the bladder wall A-delta fibers and can initiate voiding after communicating with the cerebral cortex.[6] A third brainstem nucleus, the pontine storage center, is believed to play a role in promoting continence during bladder filling by facilitating closure of the urethral sphincter.[14,15] A number of additional brain areas, including the paraventricular nucleus, periventricular nucleus of the hypothalamus, red nucleus, and raphe nucleus, also have anatomic connections with the micturition pathway but their functional connections are poorly defined.[14,16]

The pontine micturition center controls autonomic micturition function via the pontine reticulospinal tract that regulates the intermediolateral nucleus and sacral parasympathetic nucleus. The former is distributed along the intermediate gray matter of the thoracolumbar segments, which contains the sympathetic preganglionic neurons; the latter is located in the sacral intermediate gray matter, which contains parasympathetic preganglionic neurons.[14–16] In dogs, the preganglionic nuclei of the sympathetic hypogastic nerves and parasympathetic pelvic nerves are located in the intermediate gray matter of L1–L3 and S2–S3, respectively.[6] When activated, the hypogastric nerves relax the detrusor and constrict the urethra and bladder neck to facilitate bladder filling at low intravesical pressures; whereas the pelvic nerves excite the detrusor and facilitate urine voiding upon activation.[6]

Parasympathetic function relies mainly on cholinergic transmission, whereby postganglionic axonal acetylcholine release and binding with muscarinic receptors in the bladder wall result in detrusor contraction (Fig 1).[6] In contrast, sympathetic function is mediated by adrenergic transmission through the release of noradrenaline from postganglionic neuron axon terminals; noradrenaline binding with bladder wall smooth muscle β-adrenergic receptors mediates detrusor relaxation, and binding with urethral smooth muscle α1-adrenergic receptors triggers urethral contraction.[6,16]

Additionally, the cerebral cortex exerts conscious control of micturition *via* descending tracts that synapse with somatic motor neurons of the pudendal nerves in the sacral ventral horns, specifically S1–S3 in dogs, which innervate the external urethral sphincter.[6,16] Voluntary control of the external urethral sphincter is mediated by somatic cholinergic transmission; binding of acetylcholine released from pudendal nerve axon terminals with its nicotinic cholinergic receptors in the external urethral sphincter muscle produces voluntary sphincter contraction to maintain continence during bladder filling.[6,16]

Urine Storage and Voiding Mechanisms

Urine storage and periodic voiding depend upon the reciprocal relationship between reservoir and outlet,

which is mediated and coordinated by segmental spinal cord reflexes, spinal pathways and supraspinal centers. During bladder filling, the detrusor remains in a variable state of relaxation termed "compliance," allowing accommodation of increasing volumes of urine without significant increase in intravesical pressure. Gradual bladder distention stimulates the bladder wall mechanosensitive A-delta and C-fibers to produce graded potentials that: (1) stimulate the sympathetic innervation *via* hypogastric nerves to simultaneously contract the bladder outlet and inhibit the detrusor; and (2) stimulate somatic innervation of the external urethral sphincter *via* pudendal nerves to prevent leakage during bladder filling. Although areas in the lateral pons, also known as the pontine storage center or "L-region," may facilitate involuntary sphincter control, bladder filling is largely an involuntary process regulated by sympathetic thoracolumbar and somatic sacral segmental spinal cord reflexes in normal individuals (Fig 2A).[6,11,12,14,16]

In contrast, micturition is an active, voluntary process coordinated by supraspinal centers, which ensure that reciprocal detrusor contraction and outlet relaxation occur simultaneously when socially appropriate. Once a certain intravesical volume or pressure per unit volume threshold—12–32 cmH_2O in conscious humans[17–19] and 18 mL/kg or 50 cmH_2O in anesthetized dogs,[13]—is reached, the baseline afferent-graded potentials are overcome by depolarizing action potentials that convey this specific information to the pontine micturition center and the cerebral cortex.[11,12,14,15] Activation of the pontine micturition center simultaneously inhibits the sympathetic and somatic innervation to trigger bladder outlet relaxation and stimulates parasympathetic innervation to initiate and sustain detrusor contraction until urine voiding is complete (Fig 2B).

Changes in the Lower Urinary Tract after Suprasacral Spinal Cord Injury

Lower urinary tract dysfunction secondary to suprasacral spinal cord injury can result from damage at any site within the micturition pathway between the sacral segments and cerebral cortex. Experimental studies in rats and cats suggest that bladder wall C-fiber afferents, which are usually functionally silent in spinal-intact animals, can become activated after suprasacral spinal cord injury.[14,15,18,19] The ionic mechanisms underlying C-fiber neuron hyperexcitability were determined by means of patch clamp, which allows the movement of ions across transmembrane ion channels to be quantified.[20,21] Whole-cell patch clamp recordings revealed that the Na^+ channels in L6–S1 dorsal root ganglion neurons from chronic T8–T9 spinal-transected rats have lower depolarization threshold and shorter action potential duration.[20]

Changes in dorsal root ganglion Na^+ channel properties are attributed to a specific injury-induced switch in the expression of Na^+ channels in favor of those that have lower thresholds.[20] In contrast, the number of neurons innervating the bladder and the electrophysiologic

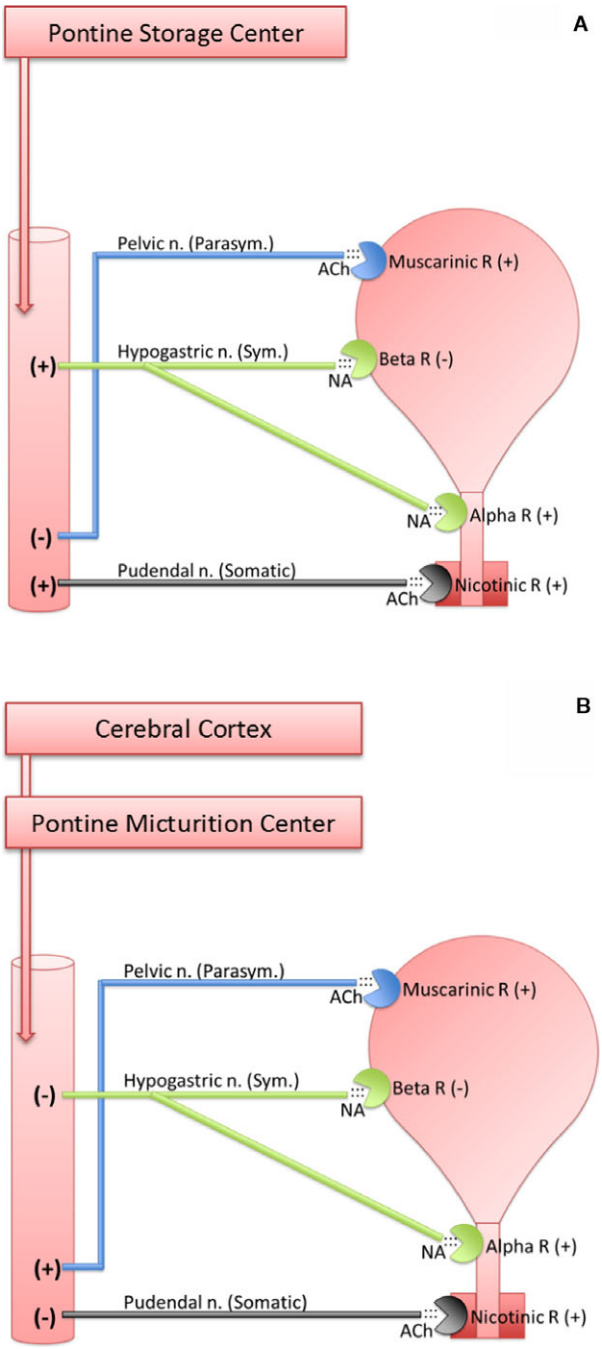

Fig 2. Reciprocal actions during urine storage and voiding: (**A**) During storage, sympathetic and somatic efferents are activated to maintain urinary continence; (**B**) During voiding, parasympathetic efferents are activated to trigger detrusor contractions.

properties of neurons innervating other pelvic organs such as the colon, both remain unchanged after spinal transection.[20] Simultaneously, at least the K_A, and possibly other subtypes of K^+ channels, are functionally incapacitated, such that application of a K^+ channel blocker 4-aminopyridine makes no difference to the movement of K^+ across the L6–S1 dorsal root ganglion neuron cell membrane.[20,21] The net effect of concurrent

Na^+ channel activation and K^+ channel deactivation is hyperexcitability of the dorsal root ganglion neurons innervating the urinary bladder.

This change in ion channel expression in dorsal root ganglion neurons can be explained by the injury-induced release of bladder neurotrophic factors such as brain-derived neurotrophic factor, glial-derived neurotrophic factor, and ciliary neurotrophic factor.[18,22] In particular, endogenous levels of nerve growth factor or NGF significantly increase in the bladder wall, lumbosacral spinal cord, and dorsal root ganglion after spinal cord injury.[18,22,23] Similarly, exogenous NGF administration can induce bladder afferent neuron firing via intravesical administration and segmental spinal cord micturition reflex via spinal cord and bladder wall administration.[20,22,24] Conversely, neutralization of endogenous NGF by intrathecal application of NGF antibodies can mitigate detrusor overactivity.[25,26]

Since it is a widely accepted concept that a target organ can exert influence on its innervating neurons, it is probable that NGF, released by the detrusor smooth muscle and urothelial cells, is responsible for the acquired bladder afferent neuron hyperexcitability by altering their ion channel properties after spinal cord injury. Indeed, hyperexcitable C-fiber-mediated spontaneous detrusor contractions and spinal cord segmental reflex voiding can be induced in chronic spinal-injured cats; this segmental reflex has a characteristic shorter central delay of 15 ms compared to the 60-ms delay in the normal supraspinal micturition reflex mediated by the spinobulbospinal pathway in spinal-intact cats.[27]

Similarly, in spinal-injured human and veterinary patients in which the supraspinal control that mediates simultaneous detrusor contraction and outlet relaxation is lost, C-fiber-mediated spinal cord segmental micturition reflex can trigger concurrent detrusor and sphincter contractions, which can in turn lead to inefficient bladder emptying, high residual volume, bladder overdistension, and detrusor hypertrophy from chronic, persistent intravesical pressure elevation.[11,12,14,15]

Furthermore, C-fiber afferent input undergoes segmental and supraspinal neuromodulation within the spinal cord and the brain before triggering the activation of autonomic and somatic efferent pathways. Spinal cord interneurons modulate both segmental micturition reflex and supraspinal communication. In response to an excitatory afferent input, the interneurons located dorsal to their efferent autonomic preganglionic neurons can in turn trigger neuronal excitation.[18,28–30] This disynaptic "afferent-interneuron-efferent" segmental reflex is thought to underlie the micturition reflex in neonates, which rely on "perineal-to-bladder" or "perigenital-to-bladder" reflex elicited by the mother licking the newborn's perineum or perigenital area.[15,28] In neonatal rats, the excitatory effect of interneurons on the autonomic preganglionic neurons can decrease by 50% during the third postnatal week, which coincides with the development of spinobulbospinal pathways.[18,28,29]

Conversely, spinal cord transection by day 14 in neonatal rats, which is before the establishment of supraspinal dominance, can free the segmental micturition reflex from supraspinal suppression.[18,28,29] Clinically, the C-fiber-mediated segmental micturition reflex can be induced by means such as intravesical cold water infusion in chronic spinal-injured human patients and in normal infants, but not in spinal-intact adults.[18,31–33] Therefore, it appears that humans and rats are naturally born with segmental spinal micturition reflexes but, as the supraspinal pathways emerge during postnatal development, the synaptic efficacy of the interneuron-mediated segmental reflex diminishes and remains suppressed unless supraspinal pathways become damaged and inherent neuroplasticity revives the dormant segmental micturition reflex.

In veterinary medicine, along with other segmental reflexes such as involuntary pelvic limb locomotive movements, "reflex voiding" or involuntary urine voiding that can be elicited by segmental afferent stimulation of the perineum, perigenital area, tail, and pelvic limbs, is commonly observed in pet dogs with chronic, severe T3–L3 spinal cord injury. These injuries can be recognized in individuals diagnosed with a modified Frankel score of 0 and exhibiting paraplegia and absence of "deep pain" sensation persisting for more than 3 months.[34] Nevertheless, these animals often require regular manual bladder expression to prevent urine retention because the development of detrusor-sphincter dyssynergia renders reflex voiding an inefficient means of urine elimination.[18]

Clinical Consequences

Spinal cord injury can affect both urine storage and voiding. After injuries to the sacral spinal cord segments, both parasympathetic and somatic innervation to the lower urinary tract can be impaired. In companion animals, the characteristic clinical signs of severe, lower motor neuron spinal cord injury are detrusor hyporeflexia or areflexia and sphincter hypotonia or atonia, which can lead to increased bladder compliance, increased bladder capacity, increased residual volume, and constant urine leakage. Similarly, in human patients, complete or severe sacral spinal cord injuries can cause detrusor and sphincter acontractility and impaired bladder sensation.[35]

In contrast, severe, acute, suprasacral spinal cord injury can abruptly disrupt intraspinal pathways, and thus eliminate the spinobulbospinal micturition reflex. The initial postinjury period termed "spinal shock" can last up to 3 months in human patients[33], but in pet dogs its effect on pelvic limb function is only apparent for 24–48 hours.[36] A similar duration of effect has been reported in experimental dogs that displayed flaccid paraplegia in the first 48–72 hours after spinal cord transection before regaining muscle tone over 14 days, whereas the return of urinary bladder tone occurred over 2–3 weeks.[37] During spinal shock, the bladder is often atonic and areflexic, meaning that urine is retained unless drained by urinary catheterization, intermittent or indwelling, or manual expression.[33,36] After spinal shock, inherent neuroplasticity mediates changes

such as the emergence of C-fiber-mediated segmental reflex in the micturition pathway occurring within weeks to months after injury; the clinical manifestation of these changes depend primarily on the location and severity of the spinal cord injury.[33,35,38]

Although the sympathetic and supraspinal regulations of bladder function such as detrusor relaxation during filling and coordinated voiding are impaired in upper motor neuron injury, the sacral parasympathetic and sacral somatic innervations remain intact, which can cause involuntary detrusor contraction during filling and uncoordinated sphincter contraction during voiding. Thus, during filling, detrusor overactivity produces periodic elevated intravesical pressure and urine leakage; whereas during voiding, detrusor-sphincter dyssynergia causes ineffective bladder emptying, high residual volume, and high intravesical pressure (Fig 3).[33]

A large proportion, 21/38 (55%), of chronically paralyzed pet dogs have detrusor overactivity, as detected by cystometry.[39] By comparison, detrusor overactivity and detrusor-sphincter dyssynergia occurs in 95% and 68% of suprasacral spinal-injured human patients, respectively.[35] These functional changes during urine storage and voiding can lead to complications, such as vesicoureteral reflux and secondary pressure-induced upper urinary tract injury, as well as increased risks for urinary tract infection.[4,40–44]

Normally, the mechanisms of continuous slow urine inflow from the upper urinary tract during bladder filling and intermittent rapid outflow during voiding prevent bacterial ascension, adhesion, and colonization within the lower urinary tract.[45] Urinary tract infections are more prevalent among spinal-injured individuals that lack the ability to clear bacteriuria efficiently because of infrequent bladder voiding, high residual volume, and the increased exposure to uropathogens that largely results from frequent urinary catheterization.[33,40,46,47] Urinary tract infections can be classified as uncomplicated or complicated; the latter suggests an underlying cause for increased susceptibility, such as immunosuppression, immunodeficiency, structural, or neurogenic outflow obstruction.[48,49]

For both complicated and uncomplicated urinary tract infections in humans and dogs, the most prevalent uropathogens are the gut *Escherichia coli* species that contaminate the periurethral area and ascend to colonize the lower urinary tract. The placement of urinary catheters can introduce periurethral and environmental pathogens into the lower urinary tract; whereas the urinary catheters themselves, especially when in-dwelling, favor bacterial attachment and multiplication, particularly when the patient requires prolonged in-hospital urinary management.[1,2,4,40,46,47] Following adhesion to urothelium, bacteria digest host cells using toxins and

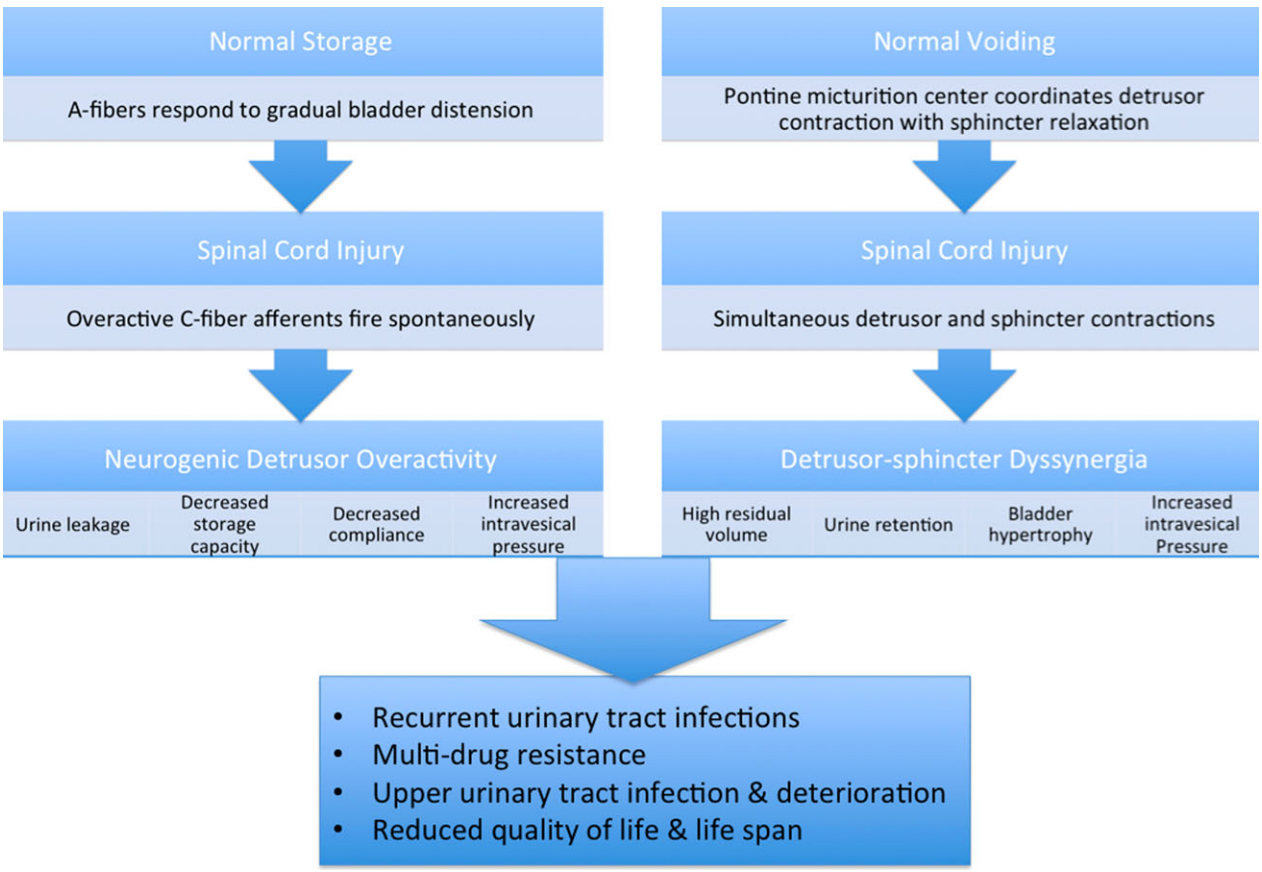

Fig 3. Clinical consequences of abnormal urine storage and voiding after severe upper motor neuron or suprasacral spinal cord injury.

proteases, multiply in host cell cytosol, and ascend to the upper urinary tract, where, if left untreated, fatal consequences such as pyelonephritis, bacteremia, and septicemia, can ensue.[1,40]

Treatment of urinary tract infection usually involves antibiotics chosen following urinalysis, urine culture, and susceptibility; frequent exposure to antibiotics can alter gut commensal microbiota and select for multidrug-resistant microorganisms.[50] Uropathogens can develop multidrug resistance shortly after antibiotic exposure by acquiring resistance-encoding plasmids such as the β-lactamase plasmids, which are capable of rapidly propagating antibiotic resistance.[51–53] Recurrences of urinary tract infection can ensue either by reascension of gut bacteria or recrudescence of a persistent urinary tract nidus such as a quiescent intercellular bacterial reservoir from a previous infection.[45] Thus, alternative therapeutic options, which will be discussed below, should be explored for the management of recurrent urinary tract infections in spinal-injured veterinary patients.

In addition to infection-induced morbidity and mortality, neurogenic outflow obstruction, and intravesical pressure elevation after spinal cord injury can lead to vesicoureteral reflux and subsequent upper urinary tract anatomic and functional deterioration. Vesicoureteral reflux is particularly common in human patients after complete upper motor neuron spinal cord injuries.[41–44] Injuries at T10–L2, where the sympathetic intermediolateral nuclei that mediate sphincter relaxation during voiding are located, are associated with the highest incidence of vesicoureteral reflux.[54]

In human patients, vesicoureteral reflux has been implicated in renal scarring identified on ultrasound examination, proteinuria, reduced glomerular filtration rate, elevated serum creatinine, reduced creatinine clearance rate, and hypertension.[55,56] Furthermore, chronic vesicoureteral reflux can impair nephrogenesis in developing kidneys.[44,57,58] In pediatric human patients, vesicoureteral reflux is associated with reflux nephropathy, chronic kidney disease, and end-stage renal disease; whereas in neonatal rodents, vesicoureteral reflux can lead to tubular cell ischemia and atrophy, glomerulosclerosis, epithelial apoptosis, and peritubular fibrosis.[42,59,60]

Lastly, although poorly investigated in veterinary patients, autonomic dysreflexia is a well-documented, potentially life-threatening condition that typically affects human patients who have chronic, severe spinal cord injuries at the level of T6 or higher.[33,57,58] Damage to the descending vasomotor pathways and sympathetic preganglionic neurons in the thoracolumbar intermediolateral nucleus and their afferent input can impair autonomic regulation of the cardiovascular function.[61] As a result, autonomic stimuli, such as distension or irritation of the urinary bladder or colon, can trigger unregulated, excessive sympathetic preganglionic neuron firing, which typically manifests as hypertension and baroreflex-mediated compensatory bradycardia; the former can increase the risk of intracranial hemorrhage.[33,57,58,62] Autonomic dysreflexia can be a permanent risk in the chronic phase of spinal cord injury in a subset of patients and often occurs as the result of autonomic or somatic stimulation below the level of the spinal cord lesion.[57,58,61,62] Thus, regular bladder and colon evacuation are recommended for the prevention of this potentially life-threatening condition; pharmacological agents such as lidocaine and bupivacaine can also be helpful.[57,58,61,62]

In conclusion, despite the similar clinical features that spinal-injured veterinary patients share with their human counterparts, many serious complications that have been extensively investigated and carefully addressed in human medicine are yet to be identified in animals.

Cystometric Evaluation of Neurogenic Lower Urinary Tract Dysfunction

Cystometry is a urodynamic procedure that measures the filling and voiding functions of the lower urinary tract. It is indicated for diagnostic and monitoring purposes in human patients who show clinical signs of urinary incontinence, including those caused by neurogenic lower urinary tract dysfunction.[63,64] Data on intravesical pressure, bladder storage capacity, detrusor overactivity, and bladder compliance can be obtained using this diagnostic tool. Furthermore, when combined with sphincter electromyogram, cystometry can be used to diagnose detrusor-sphincter dyssynergia, which is characterized by uncoordinated simultaneous contractions of the detrusor and the urethral sphincter.

In veterinary medicine, cystometry is currently uncommonly used for clinical purposes, but provides useful data for dogs enrolled in clinical studies or prehuman trials.[39] It can be performed on conscious or lightly sedated animals in lateral recumbent or standing positions using commercial urodynamic systems. A dual-lumen urinary catheter is placed aseptically, one lumen is used to measure the intravesical pressure and the other allows intravesical infusion of a sterile solution to fill the bladder. Infusion is normally stopped when leaking is apparent at the external ureteral orifice or, for patient safety, when a certain volume or intravesical pressure threshold is reached.

In severe, chronic T3–L3 spinal-injured pet dogs, detrusor overactivity can lead to altered cystometric outcome measures, especially reduced bladder compliance and capacity (Fig 4). Bladder compliance is a measure of the bladder wall response to stretching during filling and it is defined as the amount of change in intravesical pressure associated with a specific change in intravesical volume or $\Delta V/\Delta P_{ves}$. Although 12.5–30 mL/cmH_2O has been used as the lower end of normal in humans, bladder compliance can vary greatly among both spinal-intact and spinal-injured individuals, rendering its interpretation problematic.[39,63–66]

Bladder capacity can be measured by comparing the total volume infused with the maximum physiologic storage capacity. Although the generally accepted safe, intravesical pressure threshold is in the vicinity of 40–50 cmH_2O for humans,[63–67] the physiologic bladder capacity is yet to be determined, although 300–600 mL

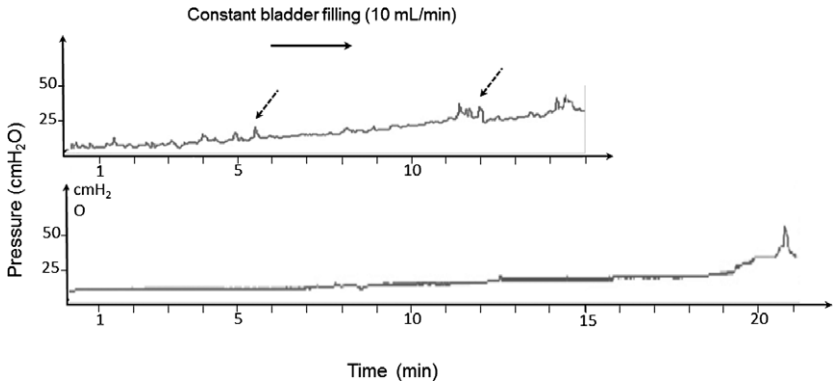

Fig 4. Cystometry recording in pet dogs with spinal cord injury. Top panel: abnormal detrusor contractions (arrows) recorded in an 8-year-old French bulldog that had intervertebral disk herniation at T13–L1 1 year previously and did not recover continence or walking. Lower panel: an unremarkable cystometry recording in a 7-year-old Beagle that had T11–T12 intervertebral disk herniation 2 years previously.

per patient has been used in most human studies.[63–67] In our cystometry studies, we have used a value of 20 mL/kg for estimating normal bladder capacity in spinal-injured pet dogs derived from a reported value of 18 mL/kg in dogs.[13]

A rectal transducer placed before infusion will simultaneously measure the abdominal pressure P_{abd}, which can be subtracted from the intravesical pressure P_{ves} to obtain the net detrusor pressure P_{det}, or $P_{ves} = P_{det} + P_{abd}$. However, the rectal transducer can produce misleading results if placed inappropriately such as contacting rectal wall or in feces.[67–70] Additionally, the rectal transducer can trigger, usually transient, detrusor contraction and subsequent voiding, defecation, and excessive pelvic limb and tail movement in T3–L3 spinal-injured pet dogs, likely because of the unsuppressed segmental afferent stimulation.

Finally, there are several difficulties with cystometry, especially when used in animals. Some examples include: (1) the typical cystometric infusion rate of 60–120 mL/kg/h used in dogs is considerably higher than the physiologic urine output rate of 1–2 mL/kg/h; (2) stress-induced confounders such as excessive abdominal movement during the procedure, typically resulting from the unfamiliar environment and handlers, can render the results difficult to interpret; (3) the body position might not be reproducible at repeated measurement sessions if the dog is uncooperative; and, (4) triggers of detrusor contraction other than bladder wall stretching such as rectal transducer placement, rapid infusion rate, and excessively cool infusion fluid temperature, all can affect the interpretation of the results.

Furthermore, in addition to catheterization-induced tissue trauma and potential ascending urinary tract infection, infusion-induced bladder distension has been documented to cause discomfort and autonomic dysreflexia in some human spinal-injured patients.[33,57,58,62,63] Thus, cystometry should be performed with caution under close observation for signs of discomfort or stress in veterinary patients. Prophylactic antibiotics can be given around the time of the procedure at the clinician's discretion.[64] Although autonomic dysreflexia is not yet an established complication in veterinary medicine, it is also advisable for dogs with cranial thoracic spinal cord injuries to have blood pressure, heart rate, and respiratory rate monitored during the procedure.

In summary, cystometry enables clinicians to objectively diagnose and monitor neurogenic lower urinary tract dysfunction. In spinal-injured individuals, cystometry is especially useful in recognizing detrusor overactivity and detrusor-sphincter dyssynergia, which can lead to many serious complications. In veterinary medicine, cystometry may become a useful part of our routine assessment of veterinary patients following acute spinal cord injury because cystometric abnormalities, such as increased storage intravesical pressure and reduced bladder compliance, are common.[39,65]

Management Considerations

The type and severity of neurogenic lower urinary tract dysfunction depend on the location and severity of the injury. Anatomically, neurogenic lower urinary tract dysfunction can be classified as: (1) suprapontine, implying primarily forebrain; (2) pontine; (3) suprasacral spinal cord; (4) sacral spinal cord; and (5) subsacral including the peripheral nerves innervating the lower urinary tract, or lower motor neuron. Collectively, the first three components constitute the "upper motor neuron."

Current long-term urological management of suprasacral spinal-injured animals is limited to treating urinary tract infections and assisting voiding, mainly by manual bladder expression. However, in paraplegic dogs, manual bladder expression is inefficient because only ~50% of the bladder volume can be emptied, resulting in substantially higher residue volumes of 0.50–33.02 mL/kg in paraplegic dogs[66] compared to the values of 0.2–0.4 mL/kg in normal dogs.[67] Thus, a consensus addressing various aspects of neurogenic lower urinary tract dysfunction, from initial diagnosis to long-term

management, should standardize and improve our current practices. The following discussion pertains to acute, traumatic T3–L3 spinal cord injuries unless otherwise stated.

Clients need to be informed as early as possible as to the degree of likely neurogenic lower urinary tract dysfunction and associated prognosis because home-based management can be challenging and time-consuming, requiring a median of 3 hours per week and up to 16 hours per week for a chronically paraplegic dog.[68] Immediately after severe acute spinal cord injury, animals can experience a period of spinal shock that is characterized by the transient absence or depression of spinal reflexes caudal to the lesion.[36] During this period, the urinary bladder passively distends but the detrusor cannot contract;[33] thus, assisted bladder voiding is often required to prevent bladder overdistension and urinary tract infection. The frequency of bladder palpation and assisted voiding by manual expression or urinary catheterization can be adjusted according to the individual patient's fluid intake; this is especially important during fluid supplementation at supraphysiologic rates such as during general anesthesia for diagnostic imaging and surgery.

It is well-established that patients may take as long as 3 months, or even more, to regain ambulation after severe acute spinal cord injury and, if it occurs, lower urinary tract function often recovers over a similar period of time. Our recent study suggests that neuroplasticity-mediated detrusor overactivity can emerge during this period in some spinal-injured pet dogs.[39] Therefore, if patients fail to regain normal micturition function after the initial spinal cord injury, owners should be informed on the likelihood and educated on the importance and practices of long-term, possibly lifelong, management of lower urinary tract dysfunction. These patients are at high risk for recurrent urinary tract infections and repeated use of antibiotics can lead to high rates of multidrug-resistant infections. To avoid this complication in dogs that appear susceptible, we would recommend using antibiotics only after culture and susceptibility testing and greater use of nonspecific urinary antiseptics, such as methanamine, nitofurantoin, and acidifiers. Periodic testing of kidney function and urine culture and susceptibility testing are advisable even in nonsymptomatic animals.

Cystometry testing forms an important part of management in human paraplegic patients and may aid in management of similarly affected dogs. In humans it is recognized to improve the decision-making process for management of incontinence and long-term outcome.[69] Cystometry might be useful to identify, at an early stage, whether manual bladder expression is successful at maintaining bladder storage capacity and normal compliance. Our recent studies have suggested that ~70% of chronic paraplegic dogs may develop low bladder compliance.[39] If these cases could be identified at an early stage, possibly within 1–3 months of injury, this problem could be averted. Similarly, identification of dogs that have very high bladder pressures could allow the potential problem of renal injury through vesicoureteric reflux and possibly secondary pyelonephritis to be averted through use of appropriate antimuscarinic drugs, as discussed below.

Current and Potential Therapies

The treatment goals for neurogenic lower urinary tract dysfunction are to stop urine leaking because of detrusor overactivity during bladder filling, to preserve upper urinary tract integrity by reducing intravesical pressure and vesicoureteral reflux, and to treat and prevent urinary tract infections.

Medical Management of Neurogenic Lower Urinary Tract Dysfunction

Antimuscarinic agents, or muscarinic receptor antagonists, such as darifenacin, fesoterodine, and oxybutynin oral medications, work by competitively binding with the bladder wall muscarinic receptors that are activated by acetylcholine-receptor binding; the parasympathetic-mediated detrusor contractions during bladder filling can be mitigated by inhibiting cholinergic neurotransmission.[70–72] The development of newer antimuscarinics with extended-release oral formulations and higher receptor selectivity has enhanced the clinical utility of this class of drugs for treating lower urinary tract dysfunction in spinal-injured human patients with suprasacral injuries.[73]

Botulinum neurotoxins such as onabotulinumtoxin-A, also known as Botoxin, intradetrusor injection also have antimuscarinic effect. Botulinum neurotoxins interfere with acetylcholine exocytosis at the parasympathetic presynaptic membrane.[70,71,74] Additionally, clinical studies suggest that bladder wall botulinum neurotoxin injection can abolish detrusor overactivity in spinal-injured individuals by reducing the urine and bladder wall nerve growth factor levels and thus activation of the hypermechanosensitive C-fiber afferents in the bladder wall.[75]

Alternatively, detrusor overactivity can be inhibited in spinal-injured human patients by directly suppressing the C-fiber-mediated bladder afferent hyperexcitability by administrating vanilloids such as capsaicin and resiniferatoxin. Vanilloid receptors, or VR1, can become upregulated after spinal cord injury.[76] After intravesical or intradetrusor delivery, vanilloid binding with the C-fiber vanilloid receptors, or transient vanilloid receptor 1, can trigger transient depolarization in the afferent neurons followed by a prolonged period of inactivation, which leads to C-fiber afferent desensitization and reduced excitability in response to bladder wall afferent input.[77–79]

Additionally, opioid receptor agonists and antagonists have been extensively investigated for treating neurogenic lower urinary tract dysfunction.[80–84] Opioid receptors are widely distributed within central nervous system micturition pathways, including locations such as the spinal cord parasympathetic nucleus, pontine micturition center and periaqueductal gray. Currently, opioids are not considered standard treatment for neurogenic detrusor overactivity and detrusor-sphincter

dyssynergia in spinal-injured human patients, due largely to their significant side-effects, which include constipation, nausea, vomiting, respiratory depression, dry mouth, drug tolerance, dependence, and addiction when administered as analgesics for treating post injury or post surgery pain and chronic central neuropathic pain,[85–88] as well as their specific impact on the neurologic outcome following acute, traumatic spinal cord injury.

For instance, in spinal-injured experimental rats, high-dose systemic morphine administration at 20 mg/kg within 24 hours post injury can lead to central neuropathic pain 3 weeks post injury; when delivered intrathecally, morphine administration can result in worse locomotor recovery and increased mortality.[89] It is thought that opioid administration can potentiate traumatic spinal cord injury-induced neuronal excitotoxicity and gliopathy, resulting in additional secondary spinal cord injury and thus worsened clinical outcome.[90–93] Moreover, opioid administration via oral, intravenous, and epidural routes have been associated with higher risks of urine retention by increasing bladder storage capacity and compliance via mechanisms including inhibition of bladder sensory innervation for detecting the degree of bladder distension, sympathetic overstimulation causing increased sphincter resistance and direct opioid binding with spinal cord opioid receptors producing detrusor relaxation.[94–98]

These opioid-induced effects on the lower urinary tract can lead to secondary complications including bladder overdistension and reduced contractility, urinary tract infections, autonomic responses, such as hypertension, bradycardia, and cardiac dysrhythmias, increased hospital stay and costs, as well as increased morbidity in human patients.[99–102] Nonetheless, experimental and early clinical evidence suggests that opioids, such as tramadol which is a weak mu-receptor agonist, U-50488 which is a kappa-receptor agonist and morphine which is a pure mu- and kappa-receptor agonist, can mitigate detrusor overactivity and detrusor-sphincter dyssynergia and improve voiding efficiency.[81–84]

Other potential therapeutic agents that target various sites within the peripheral and central micturition neuromodulatory pathways are mostly still at the experimental or early clinical stages of drug development. These potential therapeutics include agents that modulate bladder afferent ion channels such as Na^+, K^+, and Ca^{2+} ion channels, antibody treatment for reducing the levels of spinal cord injury-induced nerve growth factor, and α- and β-adrenergic agents that regulate sympathetic-mediated neurotransmission.[70,103,104]

Pharmacologic Intervention for Urinary Incontinence in the Acute Phase of Spinal Cord Injury in Dogs

Parasympathomimetic drugs such as bethanechol and carbachol have been used in dogs that have bladder atony, with the aim of contracting the detrusor, and thereby inducing urine voiding. However, there are currently no data available to confirm clinical efficacy of these drugs in treating bladder dysfunction as the result of spinal cord injury in companion animals. For instance, in one study on normal dogs, administration of bethanechol for 15 days was not associated with changes in either urethral or bladder pressure.[105] Other potential pharmacological detrusor contraction stimulators including cholinesterase inhibitors like neostigmine and pyridostigmine, beta agonists like propanalol, prostaglandin, and cisapride have not been systematically investigated in veterinary medicine.[106]

Because the smooth and striated urethral sphincters are under sympathetic and somatic nervous system control, respectively, α-sympatholytic drugs, such as prazosin, alfuzosin, and phenoxybenzamine, and striated muscle relaxants like diazepam, dantrolene, and baclofen may seem appropriate for inducing urethral sphincter relaxation and assisting urine voiding. However, experimental evidence for their efficacy is very limited. Experiments in anesthetized cats[107–109] that are already experiencing an anesthetic agent-induced muscle relaxation effect suggest that the urethral pressure changes triggered by dantrolene, dantrolene plus prazosin, prazosin, acepromazine, and phenoxybenzamine are highly variable, and are therefore not conclusively supportive of their putative effect of urethral pressure reduction.

For instance, a 20%, or 2.7 cmH_2O, reduction in urethral pressure was noted in some tests, but the clinical importance of this apparently small effect is unknown; similar experiments in conscious healthy male cats also detected considerable variation in recorded pressures and very few consistent changes in urethral pressures associated with phenoxybenzamine or diazepam administration.[107–110] On the other hand, there is some weak experimental evidence in male cats supportive of the putative urethral relaxation effect of alfuzosin,[111] as well as evidence supporting the use of prazosin in reducing urethral pressure in nonsedated healthy dogs[112] and terazosin in treating dogs with reflex dyssynergia.[113]

Surgical Management of Neurogenic Lower Urinary Tract Dysfunction

A surgical technique similar to sacral cranial root stimulation or SARS, an established surgical treatment option for human patients with detrusor overactivity and detrusor-sphincter dyssynergia,[114] is clinically available to spinal-injured pet dogs that are unable to initiate voluntary urine voiding.[115] Sacral ventral root stimulation in dogs involves the surgical isolation and placement of silicon-insulated platinum electrodes around S2 spinal nerves bilaterally. The electrodes are attached to a subcutaneous receiver coil, which can be activated transcutaneously with an external stimulator that triggers S2 firing and subsequent detrusor contraction and bladder emptying "on demand." This surgical technique provides a voiding efficiency of >90% in 8 of the 9 implanted dogs, with dogs still using the system 5 years after implantation.[115]

Sacral neuromodulation is another surgical technique, using a different type of surgical implant, that can be used for treatment of neurogenic lower urinary tract

dysfunction in spinal-injured human patients.[116] Currently it is considered a second-line treatment as an alternative to antimuscarinic agents for treating an overactive bladder.[38] Although the exact mechanisms are unknown, implant-mediated sacral nerve stimulation is thought to promote continence during bladder filling and voiding efficiency by centrally modulating the switch between urine storage and voiding.[116–118] Furthermore, detrusor overactivity and detrusor-sphincter dyssynergia can be prevented by implants that deliver bilateral stimulation via the electrodes at the S3-foramen during the acute detrusor areflexia phase that occurs during "spinal shock" in spinal-injured human patients. Sacral neuromodulation is thought to prevent the development of abnormal spinal cord segmental micturition reflex post injury by suppressing the activation of the hypermechanosensitive C-fiber afferents.[116–118]

Several other surgical options including bladder augmentation, urinary diversion, and sphincterotomy have been utilized to address neurogenic lower urinary tract dysfunction secondary to spinal cord injury but most are no longer considered a standard treatment for several reasons: (1) some, such as bladder augmentation, have been replaced by more effective medical and surgical treatment options mentioned above; (2) some, such as urinary diversion, only apply to a small subset of patients and would thus usually only be recommended if all other more established treatment options have failed; and (3) some are not favored because of their associated complications; for instance, sphincterotomy can improve voiding efficiency by reducing bladder outlet resistance but it can also lead to urinary incontinence during bladder filling.[38,116–118]

Management of Lower Urinary Tract Infection

Long-term management of complicated urinary tract infection in spinal-injured veterinary patients can be particularly challenging and costly. Multidrug-resistant uropathogen isolates are more prevalent in complicated urinary tract infections in dogs and they account for over one-third of the common uropathogens such as *Escherichia coli* and *Staphylococcus* species.[119] Therefore, urine culture and susceptibility should always be performed before starting antibiotic treatment because the long-term harm of empirical antibiotic treatment while pending culture and susceptibility results can outweigh any perceived short-term gain in systemically stable animals that might not require immediate antibiotic treatment.

Another consideration regarding the use of antibiotics for treating urinary tract infections is their urine pH-dependent efficacy. For instance, although the fluoroquinolones and aminoglycosides are most efficacious in alkaline pH conditions, tetracyclines and many β-lactams generally work better in acidic environments. On the other hand, many other drugs including clindamycin, amoxicillin, and clavulanic acid, are largely pH independent.[120] Thus, dietary or pharmacological urine pH manipulation, which is easy in clinical patients, may potentiate the efficacy of the antibiotics of choice and thus should be considered when planning treatment for complicated urinary tract infections.

Nonetheless, preventative strategies should be the focus of long-term urinary tract infection management. These include: (1) good hygiene practices to reduce gut uropathogen exposure and ascension; (2) frequent assisted bladder voiding to periodically eliminate bacteriuria and prevent bacteria adhesion; and, (3) long-term daily nonantibiotic prophylactics such as urine acidifiers like ammonium chloride and urinary tract antiseptics like nitrofurantoin, methenamine hippurate, and methenamine mandelate to render bacterial colonization and multiplication unfavorable. Although these nonantibiotic prophylactics have demonstrated efficacy in preventing the recurrence of urinary tract infections in some studies including one in which a 5.4-fold reduction during nitrofurantoin prophylaxis was reported in 219 women[121], adverse effects including nausea and acute pulmonary reactions and injuries have also been documented.[121,122]

In future, the development of novel therapies for urinary tract infection might also help with the management of spinal-injured veterinary patients. Recent human clinical trials suggest that combination therapies involving different classes of newer antibiotics, such as the combination of a third-generation cephalosporin ceftazidime and a novel non-β-lactam β-lactamase inhibitor, avibactam,[40,123] might be useful for treating multidrug-resistant uropathogens in spinal-injured veterinary patients. Many novel synthetic compounds targeting alternative aspects of the pathogenic mechanisms of urinary tract infections, such as the bacterial pili that mediate uroepithelial adhesion, are still at early stages of drug development.[124–128] In addition, bacterial pili, along with other pathogenic compounds including bacterial adhesins, toxins, proteases, and siderophores, have been the targets of antivirulence host-immunotherapy and vaccine development.[129–131]

Conclusion

The neuroplasticity-mediated pathologic changes after severe, acute spinal cord injury often impair lower urinary tract function and can significantly impact on the quality of life and life expectancy of spinal-injured veterinary patients. Clients should be informed regarding the likely severity of spinal cord injury-induced neurologic impairment and prognosis as early as possible and educated on the long-term management considerations and potential therapeutic options if their pets fail to recover by ~3 months post injury. If their efficacy can be demonstrated in well-designed, reproducible veterinary clinical trials, therapies that are designed to address common neurogenic lower urinary tract dysfunction as the result of spinal cord injury, including recurrent urinary tract infection, inability to maintain urinary continence during bladder filling, and inadequate bladder emptying, may benefit veterinary patients in the future.

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